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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,842	02/27/2004	Thomas P. Monath	06132/065003	8486

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	PAPER NUMBER
1648	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,842	MONATH ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1-4 and 8-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-7 and 25-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response and amendment filed October 24, 2006 is acknowledged and entered. Claims 1-4 and 8-24 remain withdrawn from consideration, being drawn to non-elected subject matter. Claims 5-7 and newly added claims 25-29 are under examination.

The provisional obviousness rejection of claims 5 and 6 as being unpatentable over claims 1, 2 and 4 of copending Application No. 10/345,036 is withdrawn in view of Applicant's amendment.

The objection to claims 5-7 for depending from rejected claims was made in error. The objection was made to address the need to change the dependency of claims 5-7, which were previously dependent from withdrawn claims. Applicant recognized that the Office meant to indicate that the claims were objected to for depending from withdrawn claims (not rejected claims). Therefore, the objection is withdrawn in view of Applicant's amendment.

Claims Summary

The claims as amended are drawn to a chimeric flavivirus comprising a hinge region mutation in the envelope protein of an attenuated Japanese encephalitis virus (JEV) that decreases viscerotropism of the chimeric flavivirus. The chimeric flavivirus comprises:

- capsid and non-structural proteins of a first flavivirus and
- pre-membrane (PrM) and envelope proteins of an attenuated Japanese encephalitis virus (JEV).

Specifically, the mutation in the hinge region is present in amino acids 48-61, 127-131, or 196-283 of a yellow fever virus envelope protein. It is unclear how the JEV envelope protein

mutation can be in the yellow fever virus envelope protein (see 112, second paragraph rejection below). The chimeric flavivirus is in the form of a vaccine.

When the hinge region mutation is in the JEV envelope protein, the mutation is a reversion to a wild-type sequence at envelope amino acid position 279. More specifically, the mutation at position 279 is a substitution of methionine with lysine. The attenuated JEV strain is JE-SA-14-14-2.

Oath/Declaration

The oath or declaration remains defective for reasons of record. The city of the residence of inventor Juan Arroyo has been altered but not initialed. Applicant notes that the change to the inventor's address was made by him at the time that he signed and dated the document, which should be sufficient to meet the requirements of 37 C.F.R. 1.52(c)(1). In response, the Office cannot determine whether the change to the inventor's address was made at the time that he signed and dated the document unless he dated the change. *As an alternative to filing a new oath or declaration, Applicant may submit an application data sheet with the correct information.*

Claim Objections

(*New Objection*) ***Claims 5-7 and 25-29 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.*** Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 5 requires the presence of JEV and yellow fever, yet, the dependent claims either recite a broader embodiment (flaviviruses

in general), or the claims recite redundant embodiments such as, "wherein the second flavivirus is Japanese encephalitis virus". Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

(*New Rejection*) ***Claims 5-7 and 25-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.*** The subject matter recited in the newly amended claims and the dependent claims cannot be discerned. In claim 5, the chimeric flavivirus comprises a JEV envelope protein with a hinge mutation, wherein the mutation is present in an amino acid region of a yellow fever virus envelope protein. It is unclear how the JEV mutation can be present in a yellow fever virus envelope protein. Until Applicant clarifies the identity of the chimeric flavivirus virus' components, none of the claimed embodiments can be clearly understood.

Further, the use of the phrase, "amino acids corresponding to amino acids 48-61, 127-131, and 196-283 of a yellow fever virus envelope protein", in claim 5, for example, is unclear. Specifically, the term "corresponding to" does not appear to be defined in the specification. Does the term indicate that the amino acids to be mutated are not actually in the yellow fever virus, but in the amino acids of the JEV virus that correlate to the same amino acids as the yellow fever virus envelope protein? Or, does the term indicate that the amino acids to be mutated are homologous to the amino acids of yellow fever virus? There are several potential meanings that

could be applied to the claims as amended, however, clarification and/or correction is required to determine the metes and bounds of the claimed subject matter.

(*New Rejection*) ***Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.*** The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is apparent that JEV strain JE SA 14-14-2 is required to practice the claimed invention because it is a necessary limitation for the success of the invention as stated in the claims. As a required element it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of JE SA 14-14-2. See 37 CFR 1.802. The specification does not provide a repeatable method for obtaining JE SA 14-14-2 without access to the strain itself and it does not appear to be readily available material.

Deposit of JE SA 14-14-2 in a recognized deposit facility would satisfy the enablement requirements of 35 U.S.C. 112, because the strain would be readily available to the public to practice the invention claimed, see 37 CFR 1.801- 37 CFR 1.809.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions

imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;
(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;
(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;
(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and
(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

Claims 5-7, 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. (Note that the claimed subject matter in the amended claims cannot be clearly determined, thus this rejection is made with the Office's interpretation of the claimed subject matter.) The claims as amended encompass a large genus of flavivirus chimeras having any mutation within amino acids 48-61, 127-131 or 196-283 of JEV or yellow fever virus, for which Applicant has not demonstrated adequate possession. The

embodiments that are adequately described are chimeras having the E279 reversion of Japanese encephalitis, and the substitution of lysine position 202 or 204 of Dengue virus.

The issue at hand is whether the specification provides adequate written description for the genus of mutations encompassed by the claimed chimeric JE/YF viruses. The genus of mutations includes any sort of mutation within the JEV or yellow fever virus envelope region of amino acids 48-61, 127-131 and 196-283. The specification has only described a single substitution at amino acid positions 202 or 204 of Dengue envelope that resulted in a chimeric virus that had the ability to reduce viscerotropism. These two mutations are not representative of the large genus of mutations encompassed by the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Applicant has provided a region where the mutation may be made: the hinge region of the yellow fever virus (aa 48-61, 127-131 and 196-283); or amino acids 202 or 204 of Dengue envelope protein. Given that Applicant has not provided a core structure for the mutation, or a nexus between the structure of the mutation and the claimed function (reduces viscerotropism), one of skill in the art is not put in possession of the large genus of mutations encompassed by the claims.

While one of skill in the art could test a plethora of mutations, the statue requires that the specification contain a written description of the invention, and of the manner and process of

making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention. Specifically, the specification must contain subject matter that was described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

If Applicant intends for one to test different mutations to discover which ones are suitable, then Applicant has not demonstrated possession of those mutations. The need for further discovery indicates that written description is not satisfied. If Applicant had provided a core structure for the mutation that correlates with the claimed function, then the identification of further mutations would not be unreasonable. However, the specification only provides a general region of amino acids with which one of skill in the art may test different mutations (deletion, substitution, or addition of any of the 20 amino acids, any number of amino acids, at any location in the claimed regions). Applicant's specification provides a method for searching for mutations, but appears to attempt to reach-through to the end-products of that method. The specification does not provide for the large genus of chimeric viruses claimed. Regardless of the structure of the envelope hinge region, the specification fails to provide adequate description for the genus of chimeric viruses claimed. Knowing the structure of the hinge region does not make up for not knowing which mutations are acceptable. Therefore, the claims are rejected as lacking support in the specification for the large genus of viruses encompassed.

Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily drawn to the following:

Applicant notes that the claims have been amended to specify that the viruses of the chimeric viruses that include an envelope protein from an attenuated JEV, which includes a hinge region mutation in any one (or more) of amino acids corresponding to amino acids 48-61, 127-131 and 196-283 of a yellow fever virus, that decreases viscerotropism of the chimeric flavivirus.

In response to Applicant's amendment, the genus of mutations includes any sort of mutation within the JEV or yellow fever virus envelope region of amino acids 48-61, 127-131 and 196-283. The specification has only described a single substitution at amino acid positions 202 or 204 of Dengue envelope that resulted in a chimeric virus that had the ability to reduce viscerotropism. These two mutations are not representative of the large genus of mutations encompassed by the claims. Given that Applicant has not provided a core structure for the mutation, or a nexus between the structure of the mutation and the claimed function (reduces viscerotropism), one of skill in the art is not put in possession of the large genus of mutations encompassed by the claims.

Applicant notes that the flavivirus envelope hinge region is well defined in the art, evidenced by Rey *et al.*, (*Nature*, 1995, 375:291-298), which discloses a crystal structure of this region of a representative flavivirus. Applicant also points to a diagram showing the envelope structure of JEV, prepared by homology modeling using the structure described in the Rey reference.

In response to Applicant's argument, the Office has considered the Rey *et al.* reference, but has not received the referenced diagram. Regardless of the structure of the envelope hinge region, the specification fails to provide adequate description for the genus of chimeric viruses

claimed. Knowing the structure of the hinge region does not make up for not knowing which mutations are capable of decreasing the viscerotropism of the chimeric virus. Without identifying a representative number of species, the larger genus of chimeric viruses having the claimed range of mutations is not adequately provided for. Therefore, the rejection is maintained for reasons of record.

Claim Rejections - 35 USC § 102

Claims 5-7 and 25-29 are rejected under 35 U.S.C. 102(b) as being anticipated by "Chambers" (J. Virology, 1999, 73(4):3095-3101). Note that the claims are rejected based on the Office's understanding of the claimed subject matter (see the 112 second paragraph rejection). Chambers discloses the production of a chimeric yellow fever/Japanese encephalitis virus comprising structural proteins prM and E of JEV within the backbone of a molecular clone YF17D (abstract). The yellow fever virus background naturally comprises capsid and non-structural proteins. The JEV envelope region has a mutation (*i.e.*, reversion) at position 279 in the hinge region (see Tables 3-4).

Applicant argues that the chimeric flavivirus described in the Chambers reference include envelope sequences of the attenuated SA 14-14-2 strain or the wild-type Nakayama strain. Applicant argues that the SA 14-14-2 sequences do not anticipate the present claims because the envelope hinge region sequences of these chimeras do not include mutations that decrease viscerotropism. Applicant also argues that the chimeras including the Nakayama sequences also do not anticipate the present claims because the envelope proteins of these chimeras are not from an attenuated strain.

In response to this argument, Chambers discloses that the JEV envelope region has a mutation (*i.e.*, reversion) at position 279 in the hinge region (see Tables 3-4). This mutation is expected to result in decreased viscerotropism of the chimeric virus. As noted above, the rejection is made according to the Office's interpretation of the claimed subject matter.

Claims 5-7 and 25-29 are rejected under 35 U.S.C. 102(b) as being anticipated by "Arroyo" (J. Virology, 2001, 75(2):934-942). The claims are summarized above. Arroyo discloses a yellow fever virus/Japanese encephalitis virus chimera comprising a yellow fever virus vaccine strain/JEV Nakayama flavivirus having a lysine at position 279 in the hinge region (Table 2). Therefore, the disclosure of Arroyo anticipates the invention as claimed.

Applicant argues that Arroyo does not suggest the use of the revertants, such as the E279 revertant in the form of vaccines. Applicant also argues that Arroyo discloses that the reversion at E279 appeared to increase neurovirulence. Thus there would not have been any motivation to use the E279 in a vaccine.

In response to Applicant's arguments, the claims' recitation, "in the form of a vaccine" does not impart any meaning to the claimed invention because there are no structural components to the "form of the vaccine". Even if the claims recited, "A chimeric flavivirus vaccine", the structural components of the claims are met by Arroyo. Any function of Applicant's product is expected to be present in Arroyo's product. The Office notes that the claims are drawn to products, not methods of use. The art rejection relies on the components of claims, not the function of the components since the components inherently possess whatever activities are discovered about them. Therefore, the rejection is maintained for reasons of record.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The

examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Stacy B. Chen 12/24/06

STACY B. CHEN
PRIMARY EXAMINER

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